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Stroke Risk Factors Beyond the CHA_2DS_2-VASc Score: Can We Improve our Identification of 'High Stroke Risk' Patients with Atrial Fibrillation?

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Abstract

The prevention of stroke and other thromboembolic events plays a crucial role in the management of atrial fibrillation (AF) patients. Not all AF patients are equal in terms of thromboembolic risk, therefore not all will benefit from oral anticoagulation treatment. The general principle is that the expected benefit of anticoagulation in reduction of thromboembolic risk must exceed the expected harm caused by possible bleeding. Some guidelines have focused on a categorical approach to stroke prevention, with a focus on identifying high risk patients for oral anticoagulation (OAC). Various current guidelines recommend assessment of stroke risk using the $CHADS_2$ or CHA_2DS_2-VASc scores in order to initially detect low-risk patients, who require no antithrombotic therapy. However, the scores do not incorporate all possible risk factors causing a high thromboembolic risk. Factors such as impaired renal function, obstructive sleep apnea, echocardiographic and biochemical or coagulation parameters can also predict adverse thromboembolic events. The present review aims to describe biomarkers whether blood, urine, imaging (cardiac or cerebral) or clinical that go beyond the CHA_2DS_2-VASc score and potentially aid stroke risk assessment. Whilst useful in some cases, the presented parameters should be perhaps used to further refine initial identification of low risk patients, following which effective stroke prevention can be offered to those with ≥1 additional stroke risk factors.

Key words: atrial fibrillation; CHA_2DS_2-VASc; $CHADS_2$; thromboembolic risk; stroke

Introduction

Atrial fibrillation (AF) is an independent risk factor for stroke, but not all AF patients have equal stroke risk and therefore, not all should be considered in the same manner. Age, sex and comorbidities influence thromboembolic risk, and it would be simplistic to regard that all risk factors carry equal weight. Various stroke risk factors had led to a development of several risk stratification scores, to aid clinical decision-making. The general principle is that the expected benefit in reduction of ischemic stroke risk associated with anticoagulation must exceed the expected bleeding-related harm. Many of the current guidelines of many scientific societies enforce making the decision on whether to use anticoagulation therapy on 1 of the 2 most widely used risk-stratification schemes, that is, the $CHADS_2$ or CHA_2DS_2-VASc scores. However, these scores were designed to be simple and practical, and thus, include the common stroke risk factors seen in everyday clinical practice. These scores do not include many of the less common stroke risk factors, imaging or biomarkers, and in this review article, we aim to look beyond the common stroke risk factors within these 2 clinical risk scores.

$CHADS_2$ and CHA_2DS_2-VASc scores: where are we now?

Over the last few decades several epidemiological studies aimed to describe factors influencing the stroke risk in AF patients. The $CHADS_2$ score was developed from the risk factors for stroke seen in the non-warfarin arms of the historical trials cohorts, amalgamating the risk stratification schemes of the AF Investigators and the SPAF Investigators [1]. The $CHADS_2$ score was validated in the hospitalised cohort of the National Registry of Atrial Fibrillation (NRAF) study. Using the $CHADS_2$ score, points are assigned for history of (recent decompensated) Congestive heart failure, Hypertension, Age $\geq$ 75 years, Diabetes mellitus and history of Stroke or transient ischemic attach. The $CHADS_2$ score was simple,

and promptly found its place in clinical practice. Over the years following its introduction, the limitations of the $CHADS_2$ score were increasingly evident [2, 3]. Indeed, external validations of the score and reviews that compared $CHADS_2$ with other risk assessment schemes confirmed the poor ability of the $CHADS_2$ score in distinguishing 'high risk' patients who will benefit from anticoagulation [2, 4]. Also, the $CHADS_2$ score poorly identified low-risk patients [5], resulting in high rates of thromboembolic events even in presumably low-risk patients.

In 2010, the CHA_2DS_2-VASc was proposed, which incorporated factors omitted in the original $CHADS_2$ score but included additional 'non-$CHADS_2$ risk factors', namely age 65-74, vascular disease (myocardial infarction, peripheral artery disease, complex aortic plaque) and female sex [6] [Table 1]. Many subsequent analyses showed that the CHA_2DS_2-VASc particularly helped distinguish patients who were at low-risk where antithrombotic therapy was not indicated. Table 2 summarises the annual stroke and thromboembolism risk according to the $CHADS_2$ and CHA_2DS_2-VASc scores [7].

Given that risk scores solely based on clinical risk factors only have modest predictive value for high risk patients, and that prior guideline strategies focused on a categorical (that is, low, moderate and high) risk strata approach to stroke prevention led to under-treatment of the high risk patients, a different focus was clearly needed. In addition, stroke risk is a continuum, and the artificial categorization of stroke risk into low, moderate and high risk strata simply had not improved optimal thromboprophylaxis amongst AF patients, especially amongst the 'high risk' category [5].

The approach associated with the introduction of CHA_2DS_2-VASc score changed clinical practice. In the 2012 focused update of the European Society of Cardiology guidelines, there was a recommendation that instead of focusing on the identification of high risk patients, a clinical practice shift was recommendation so that the initial step was the

identification of 'truly low risk' patients (that is, CHA_2DS_2-VASc score 0 in males, 1 in females) who did not need any antithrombotic therapy. The subsequent step was to offer effective stroke prevention (i.e. oral anticoagulation) to patients with 1 or more additional stroke risk factors. Indeed, Olesen et al. found that a $CHADS_2 = 0$ was not 'low risk' and that the annual stroke risk in this group may be as high as 3.2% [8].

Guidelines do differ in their approaches. In the European Society of Cardiology and American Heart Association/American College of Cardiology/Heart Rhythm Society (AHA/ACC/HRS), the use of CHA_2DS_2-VASc score is recommended [9, 10]. However, in the European Society of Cardiology guidelines only patients with CHA_2DS_2-VASc score = 0 in males (or 1 in females) are not recommended oral anticoagulation, while all the others with ≥1 stroke risk factors a recommended (or should consider) oral anticoagulants. The 2014 AHA/ACC/HRS agree with no anticoagulation in patients with CHA_2DS_2-VASc score = 0, but in those with a CHA_2DS_2-VASc score = 1 the recommendation is 'nothing, aspirin or oral anticoagulation'.

The guidelines of the Canadian Cardiovascular Society and the American College of Chest Physicians also opt for using the $CHADS_2$ score [11, 12]. Again, they also agree on no coagulation in $CHADS_2 = 0$ patients, but the Canadian Cardiovascular Society assigns oral anticoagulation to all patients with a score ≥1 or those age ≥65 years, with aspirin recommended in AF patients age <65 years with vascular disease. The 2012 American College of Chest Physicians guidelines are based on the $CHADS_2$ score, but in those with a $CHADS_2$ score = 0, they recommend consideration of 'non $CHADS_2$' risk factors (i.e. age 65-74, vascular disease and female gender) where oral anticoagulation may be considered. Details regarding the differences in all 4 guidelines are described in Figure 1 [13].

Beyond the CHA_2DS_2-VASc score

As discussed above, the CHA_2DS_2-VASc score includes the common stroke risk factors seen in everyday clinical practice. Apart from left ventricular impairment or complex aortic plaque on echocardiography, the CHA_2DS_2-VASc score does not include any imaging or biomarker parameters, nor some of the less common clinical stroke risk factors.

Impaired renal function

Chronic kidney disease is common in AF patients, and between 10 and 15% of all AF patients meet the criteria for the diagnosis [9]. The prevalence of AF also rises with the severity of renal function impairment. For example, amongst AF patients with estimated glomerular filtration rate <45 ml/min, the prevalence of AF was approximately 20% [14]. Common risk factors are responsible for development of both AF and chronic kidney disease – indeed, these include hypertension, diabetes mellitus, impaired endothelial function and inflammation, and all are associated with elevated thromboembolic risk.

Impaired renal function impairment is associated with increased thromboembolic risk in AF. For example, in female patients with AF, a history of stroke or transient ischemic attack has been linked with 7-fold increase in the stroke risk, whilst renal dysfunction resulted in an 11-fold increase [15].

One analysis of AF patients categorized according the risk assessed in the $CHADS_2$ score found that in the control group (patients with normal renal function) approximately 70% of patients were classified as $CHADS_2$ 0 or 1 points, while in the group with CKD stage >III almost 70% had $CHADS_2 \geq 2$ points [16]. This accentuated risk with chronic kidney disease in AF patients led to a proposal to include chronic kidney disease into the existing CHA_2DS_2-VASc scheme, whereby the little “c” on the end of the acronym was proposed to be translated as “chronic severe renal impairment” [17].

In the interim, the R_2CHADS_2 score was proposed based on an analysis of the

ROCKET AF study [18]. The initial "R_2" in the acronym stood for renal dysfunction and meant that a patients was assigned 2 additional point when his glomerular filtration rate was <60 mL/min. The initial analysis showed that the predictive value of this score was comparable to $CHADS_2$ and CHA_2DS_2-VASc, but has several major limitations. Also, the derivation of R_2CHADS_2 was from a selected anticoagulated clinical trial cohort, which only included high risk subjects ($CHADS_2$ score ≥2, and those with score=2 were capped at 10%) and those with creatinine clearance <30 mL/min were excluded.

Various 'real world' cohorts with a broad spectrum of stroke risk and renal function showed that renal function did not significantly improve the prediction value of the CHA_2DS_2-VASc score for identifying high risk patients. For example, Roldán et al. showed that adding chronic kidney disease to $CHADS_2$ nor CHA_2DS_2-VASc in AF patients did not provide additional benefit in risk stratification [19]. Renal impairment is associated with heart failure, age, diabetes, vascular disease, etc. – which are components within the CHA_2DS_2-VASc score. Thus, it would be difficult to show an incremental predictive advantage in stroke prediction by adding renal impairment to CHA_2DS_2-VASc.

There is little doubt that chronic kidney disease in AF patients represents a high risk group. For example, Lin et al. identified 338 individuals with CHA_2DS_2-VASc score of 0–1 points and followed them for systemic thromboembolic events, including acute ischemic stroke, transient ischemic attack, and peripheral artery embolism [20]. In low-risk patients without the chronic kidney disease annual event rate was 0.2%, whereas with chronic kidney disease patients the event rate was 2.9% ($p<0.001$). Similar conclusions were evident in a study of patients after AF ablation [21], where in patients with CHA_2DS_2-VASc score of 0–1 presence of chronic kidney disease was associated with a 14-fold increase in the rate of thromboembolic events. Therefore all AF patients with chronic kidney disease are at increased risk of thromboembolic events.

Obstructive sleep apnea

Obstructive sleep apnea is among the more novel cardiovascular risk factors, associated with a number of cardiovascular diseases, including hypertension, coronary artery disease, myocardial infarction, stroke or arrhythmias. This translates into elevated risk of stroke seen in but this seems to be related to several factors, including a prothrombotic state, but endothelial dysfunction, intermittent hypoxia, variations in intrathoracic pressure, and recurrent arousals associated with increased heart rate and blood pressure [22].

The prevalence of obstructive sleep apnea amongst AF patients is very high. In the general population, the estimated obstructive sleep apnea prevalence is 2-4%, while in AF patients referred for ablation, obstructive sleep apnea was found in nearly 46% of cases [23]. Recently, obstructive sleep apnea and AF, along with erectile dysfunction, have been proposed to be a single clinical entity. [24]

Obstructive sleep apnea is directly and independently associated with elevated thromboembolic risk in AF. Our study included 254 AF patients who underwent polygraphy for a diagnosis of OSA and had their thromboembolic risk assessed using the $CHADS_2$ and CHA_2DS_2-VASc scores [25]. The patients with obstructive sleep apnea had significantly higher $CHADS_2$ and CHA_2DS_2-VASc scores, and with along with the increasing obstructive sleep apnea severity – expressed by higher values of the apnea-hypopnea index, also the mean risk score rose. A paper by Yaranov et al. [26] found that in patients with CHA_2DS_2-VASc = 0, the presence of obstructive sleep apnea increased the risk of stroke by 62%.

Other clinical risk factors associated with increased thromboembolism

Amyloid is a fibrous protein aggregate composed of various form of inappropriately folded proteins and polypeptides. It is associated with degenerative diseases of central

nervous system and the heart. One of its sub-forms - serum amyloid protein A is considered to be an inflammatory cytokine. Elevated serum amyloid protein A levels have been found in AF patients and are associated with atrial remodelling and inflammatory state and promotes vascular thrombosis. This association is confirmed by higher levels of serum amyloid protein A found in patients with venous thromboembolism compared to control group. A different type of the protein, namely β-amyloid is extensively deposited within the walls of small vessels, especially in the elderly. The presence of amyloid angiopathy in the cerebral vessels predisposes to higher risk for thromboembolic events but also for intracranial hemorrhage related to anticoagulation [27].

Also, some myocardial disease like obstructive hypertrophic cardiomyopathy (HC) are linked with alterations in coagulation parameters. In obstructive HC patients various indicators of the coagulation activation are found. They include elevated levels of plasma fibrinopeptide A and thrombin-antithrombin HI complex. Nearly 15% of HC patients develop AF, and such patients are at high risk of stroke and thromboembolism [28]. Others have proposed the addition of hyperlipidaemia and smoking to CHA_2DS_2–VASc, the so-called CHA_2DS_2-VASc-HS score, proposed in order to predict vascular events, not thromboembolism [29].

Echocardiography

Echocardiography is among the most often used imaging techniques used in AF patients. Transesophageal echocardiography is a method more accurate in assessing left atrial appendage size, function and presence of thrombus. It is routinely used prior to cardioversion or catheter ablation to prevent procedure–related thromboembolism. Nevertheless, the transthoracic echocardiography also plays a role in the thromboembolic risk stratification of AF patients. Transthoracic echocardiography is a method more accessible and more often

used. Recent guidelines of the National Institute for Health and Clinical Excellence (NICE) state that transesophageal echocardiography may help in assessment of patients, in whom refinement of clinical risk stratification for antithrombotic therapy is needed. [30]

Utility of both imaging techniques in the stroke assessment has been proven in numerous studies, which are briefly summarized in the Table 3 (modified from Providência et al. [31]). Most of the prognostic factors described in the literature are associated to the left atrium morphology and function.

As we have recently shown, the simplest measurement derived from left atrial diameter is a good predictor of thromboembolic risk [40], whereby atrial enlargement is not only related to the higher risk scores, but similarly as in the case of obstructive sleep apnea, the thromboembolic risk rises along with the rising left atrial size.

There is a relation between $CHADS_2$ and CHA_2DS_2-VASc scores and left atrial remodelling status including its maximum volume index, total emptying fraction and mean strain [31]. Other described echocardiographic parameters include mechanical discordance, electromechanical delay or increased orifice size and decreased flow velocity of left atrial appendage, spontaneous contrast, smoke, sludge, or thrombus [41].

Biomarkers

There have been a wide plethora of biomarkers that have been tested in AF, and have been related to prognosis and stroke risk in AF. These biomarkers include those related to myocardial stress or injury (i.e. troponins, natriuretic peptides), altered coagulation (D-dimer, plasminogen activator inhibitor, tissue factor, P-selectin), endothelial damage/dysfunction (thrombomodulin, E-selectin, von Wilebrand factor), inflammation (C-reactive protein, interleukin-6, tumour necrosis factor-α), fibrosis and extracellular matrix turnover (transforming growth factor-β, myeloperoxidase, metallopeptidases and their inhibitor) or

genetic factors (micro RNA, single-nucleotide polymorphisms) [42].

Stroke and thromboembolic events in AF patients are caused mainly by alteration in the 3 components of Virchow's triad, as follows: (i) abnormal blood flow (blood stasis in the left atrium), (ii) vessel wall abnormalities (endothelial and endocardial damage/dysfunction, oxidative stress) and (iii) abnormal blood constituents.

Table 4 (modified from Kornej et al. [42]) shows a wide spectrum of the biomarkers that have been associated with stroke or adverse thromboembolic events in patients with AF [Table 4]. Of course, a balance is needed between complex additional biomarker tests that require time and generate costs, and practical simplicity of risk prediction schemes used in clinical practice in busy wards or clinics. Thus, more emphasis now put on the initial identification of "truly low risk" patients, and therefore biomarkers with high negative-predictive value for ruling out thrombosis may be particularly useful.

Endothelial damage/dysfunction often measured by levels of circulating von Wilebrand factor was the first biomarker shown to help refined clinical risk stratification in AF, improving the predictive value of the $CHADS_2$ and Birmingham scores [57]. Other factors include uric acid that was also useful in refining risk assessment [58]. The addition of troponin to risk assessment scheme similarly helped identify patients with higher risk of intracardiac thrombi as seen on the echocardiography [59]. Another marker of myocardial stress, that is, N-terminal pro–B-type natriuretic peptide provides complementary prognostic information to the CHA_2DS_2–VASc score [60]. More recently, growth differentiation factor 15 a novel marker of oxidative stress and inflammation was tested in an anticoagulated clinical trial population [61]. Higher growth differentiation factor 15 concentrations were associated with a risk stroke or systemic embolism, major bleeding and death, and the association in this selected trial cohort remained significant after adjustment for risk factors included in the CHA_2DS_2-VASc score.

Adding large number of biomarkers (listed in table 5.) may help improve prediction of 'high risk' but would be at the cost or disadvantage of adding substantial complexity, expense and lack of practicality especially where rapid decisions are needed. [Table 5] Extensive and complex biochemical, imaging, and physical assessment are perhaps not mandatory in every AF patient to decide on anticoagulation. Whilst useful in some cases, the presented parameters should be perhaps used to further refine the initial identification of low risk patients, following which effective stroke prevention can be offered to those with ≥1 additional stroke risk factors. Proposed scheme for the AF patients screening for additional non-CHA_2DS_2-VASc risk factors is proposed in the figure 2. [Figure 2]

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Figure legends.

Figure 1. Comparison of risk assessment schemes used in different guidelines [21].

Figure 2. Proposed flow-chart for thromboembolic risk assessment in atrial fibrillation patients.

ACCP – American College of Chest Physicians, AHA/AC/HRS – American Heart Association/American College of Cardiology/Heart Rhythm Society, CCS – Canadian Cardiovascular Society, CKD – chronic kidney disease, CrCl – creatinine clearance, ESC - European Society of Cardiology, vit. K – vitamin K.

Table 1. Comparison of the $CHADS_2$ and CHA_2DS_2-VASc scores.

LVEF – left ventricular ejection fraction

**criteria from the validation study*

$CHADS_2$			**CHA_2DS_2-VASc**	
Description*	Points	Letter	Points	Description*
Recent heart failure exacerbation	1	**C**	1	Moderate to severe systolic left ventricular dysfunction, LVEF ≤40%, or recent decompensated heart failure requiring hospitalization
History of hypertension	1	**H**	1	History of hypertension
Age ≥75 years	1	**A**	2	Age ≥75 years
Diabetes mellitus	1	**D**	1	Diabetes mellitus
History of stroke or transient ischemic attack	2	**S**	2	History of stroke, transient ischemic attack or thromboembolism
		V	1	History of myocardial infarction, complex aortic plaque or peripheral artery disease
		A	1	Age 65 to 74 years
		Sc	1	Female sex

Table 2. Comparison of the annual hospital admission and death rates due to thromboembolism (includes peripheral artery embolism, ischaemic stroke, and pulmonary embolism) as assessed by $CHADS_2$ and CHA_2DS_2-VASc scores.

$CHADS_2$		**CHA_2DS_2-VASc**
Annual risk	Points	Annual risk
1.7% (1.5-1.9)	**0**	0.8% (0.6-1.0)
4.8% (4.5-5.1)	**1**	2.0% (1.7-2.4)
7.3% (6.9-7.8)	**2**	3.7% (3.4-4.1)
15.5% (14.6-16.4)	**3**	5.9% (5.5-6.3)
21.6% (20.0-23.2)	**4**	9.3% (8.7-9.9)
19.7% (16.9-23.0)	**5**	15.3% (14.4-16.2)
22.4% (14.6-34.3)	**6**	19.7% (18.2-21.4)
	7	21.5% (18.8-24.6)
	8	22.3% (16.3-30.8)
	9	23.6% (10.6-52.6)

Table 3. Echocardiography parameters in prediction of various thromboembolic events in atrial fibrillation patients.

Study	Year	Number of participants, type of AF	Parameter	Main findings
TRANSTHORACIC ECHOCARDIOGRAPHY				
SPAF Investigators [32]	1992	568 + non-rheumatic	14 transthoracic variables i.e. LA size, LV posteriori wall, LV end diastolic/systolic dimensions, regional dysfunction	LA size and depressed LVEF were independent predictors of thromboembolism
Osranek et al. [33]	2005	46 + lone	LA volume index, LV ejection fraction	LA volume ≥32 mL/m^2 was associated worse event-free survival
Lee et al. [34]	2008	330 + persistent	E/E' ratio	E/E' ratio was independently associated with ischemic stroke
Shin et al. [35]	2010	148 + AF and heart failure with preserved EF	S' and E'	S' and E', were predictors of a composite of cardiovascular death, recurrent heart failure, and ischemic stroke
Azemi et al. [36]	2012	57 + non-valvular	LA strain	Reduced peak negative and peak positive LA strain values in patients with stroke
TRANSESOPHAGEAL ECHOCARDIOGRAPHY				
Zabalgoitia et al. [37]	1998	789 + non-valvular	LA appendage thrombi, dense SEC, LA appendage peak flow velocities ≤20 cm/sec, complex aortic plaque	All factors were associated with increased thromboembolic risk
SPAF Committee on Echocardiography [38]	1998	382 + non-valvular	LA abnormality, complex aortic plaque, LA appendage abnormality	LA abnormality, complex aortic plaque, LA appendage abnormality was associated with high risk for stroke
Dawn et al. [39]	2005	175	LA appendage thrombus, LA SEC	LA appendage thrombus and LA SEC were predictors of cardiovascular death

AF, atrial fibrillation; LA, left atrium; LV, left ventricle; LVEF, left ventricular ejection fraction; SEC, spontaneous echocardiographic contrast; SPAF III, Stroke Prevention in Atrial Fibrillation III;

Table 4. Biomarkers in prediction of various thromboembolic events in atrial fibrillation patients

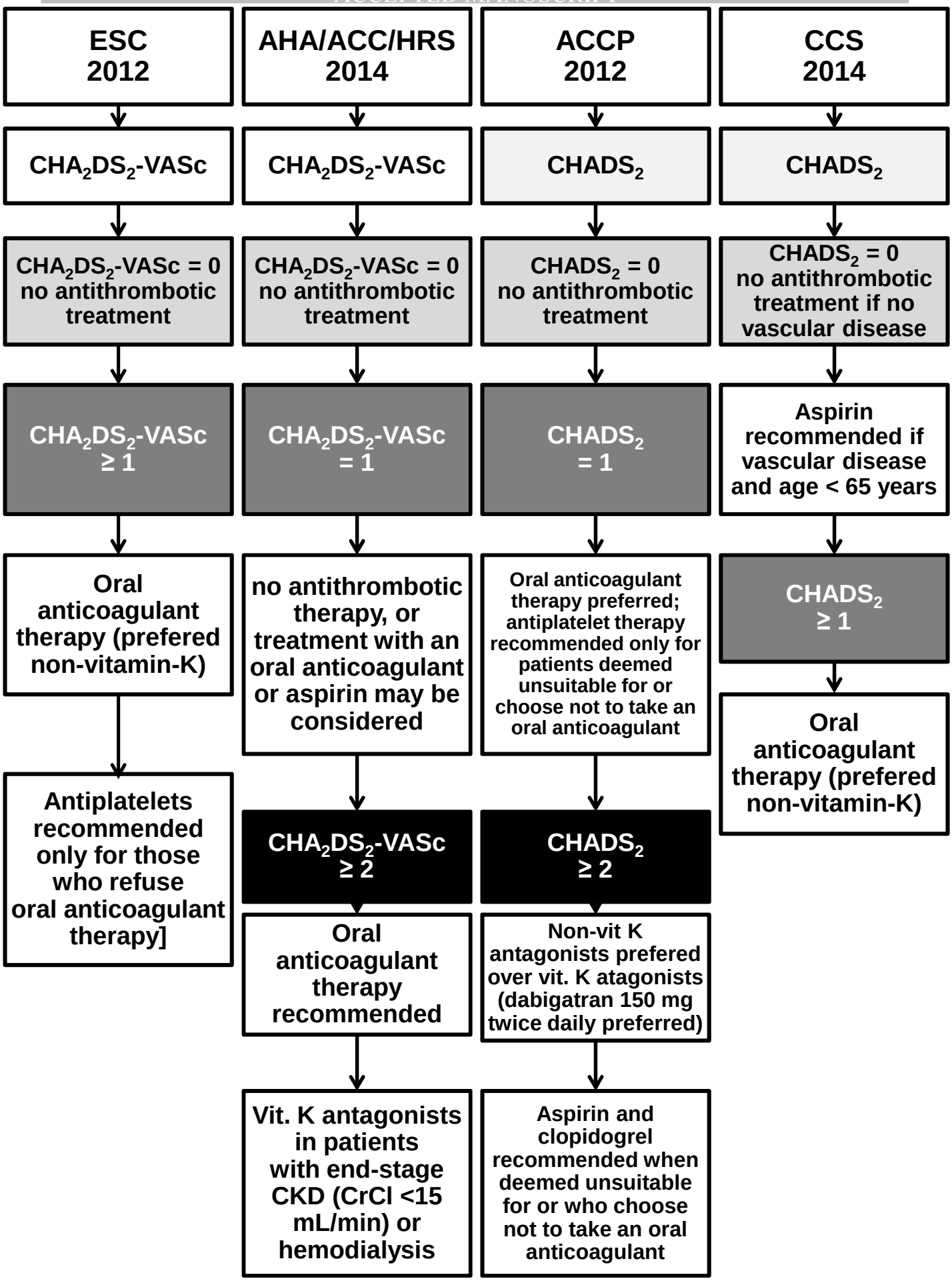
Study	Year	Participants	Biomarker	Investigation
Heppell et al. [43]	1997	109	BTG, von Wilebrand factor	Association with presence of left atrial thrombosis
Mondillo et al. [44]	2000	45 chronic AF, 35 control	von Wilebrand factor, thrombomodulin	Higher levels in chronic AF; association with a prothrombotic state and endothelial dysfunction, coagulation factors and left atrial dimension
Conway et al. [45]	2003	994 AF patients taking aspirin	von Wilebrand factor, P-selectin	Rise in von Wilebrand was predictive of stroke and vascular events
Conway et al. [46]	2004	106 AF; 41 control	Interleukin 6, CRP, TF	Higher levels in AF patients; TF associated with stroke risk
Heeringa et al. [47]	2006	162 AF, 324 control	P-selectin	Association with adverse outcomes in AF
Nozawa et al. [48]	2006	509	D-dimer	Prediction of thromboembolic events even in AF patients on anticoagulation
Ferro et al. [49]	2007	285	CD-40 ligand	Predictor of vascular events (stroke and myocardial infarct)
Lip et al. [50]	2007	880	hsCRP	Correlation with stroke risk factors and prognosis (mortality, cardiovascular events)
Kurl et al. [51]	2009	958	NT-proBNP, NT-proANP	Predictor for stroke and AF in men
Pinto et al. [52]	2009	373	TNF-a, IL-6, von Wilebrand factor	Predictor for new-onset stroke in persistent AF
Yuce et al. [53]	2010	205 chronic AF	MPV	MPV is not related with left atrial thrombus in patients with chronic AF
Sadanaga et al. [54]	2011	261	BNP	Association with thromboembolic events in patients with AF during oral anticoagulant therapy
Hijazi et al. [55]	2012	6 189	NT-proBNP, Troponin I	Association with risk for stroke and mortality

AF, atrial fibrillation; BTG, β-thromboglobulin; CHF, chronic heart failure; CRP, C-reactive protein; HF, heart failure; hsCRP, highly sensitive C-reactive protein; IL, interleukin; LAA, left atrial appendage; MMP, metallopeptidase; MPV, mean platelet volume; NT-proANP, N-terminal prohormone of ANP; NT-proBNP, N-terminal prohormone of BNP; OAC, oral anticoagulants; SPAF III, Stroke Prevention in Atrial Fibrillation III; TF, tissue factor; TNF, tumour necrosis factor;

Table 5. Some of the factors associated with an increased thromboembolic risk, that are not issued in the CHA_2DS_2-VASc score.

NT-proBNP, N-terminal pro-B-type natriuretic protein

Factors associated with an increased thromboembolic risk, that are not issued in the CHA_2DS_2-VASc score
- chronic kidney disease
- obstructive sleep apnea
- left atrial enlargement
- left atrial strain
- atrial mechanical discordance, electromechanical delay or increased orifice size
- decreased flow velocity of left atrial appendage
- echocardiographic spontaneous contrast, smoke, sludge, or thrombus
- troponin
- NT-proBNP
- adiponectine
- D-dimer
- smoking



Patient with non-valvular AF

Assess thromboembolic risk risk using the CHA_2DS_2-VASc score

CHA_2DS_2-VASc ≥ 1 in men
or
CHA_2DS_2-VASc ≥ 2 in women

YES → **Anticoagulation treatment, preferably NOAC**

NO

Perform additional risk assessment:

- **for OSA** (medical history, physical examination, Epworth sleepiness scale or polysomnography)
- **for renal function impairment** (creatinine, glomelular filtration rate)
- **for LA thrombus,** other ECHO indices of thromboembolic risk (TTE and/or if applicable TEE)
- **for biochemical thromboembolism biomarkers** (uric acid, lipids, D-dimer, BNP, NT-proBNP, vWF, and others, where available)
- **for other risk factors** feasible in real-life risk stratification (i.e. dyslipidemia, smoking etc.)

Many / one strong additional thromboembolic risk factor

YES --------> **Consider anticoagulation treatment, preferably NOAC**

NO

Do not use anticoagulation treatment